DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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APR 14 2009

Mr. Anthony C. Celeste
Senior Vice President
Kendle International
Kendle Regulatory Affairs
7361 Calhoun Place, Suite 500
Rockville, MD 20855

Re: Docket No. FDA-2007-P-0250

Dear Mr. Celeste:

This letter responds to your citizen petition dated September 13, 2007, submitted under 21 CFR 10.30 on behalf of Sun Pharmaceuticals Industries Limited, requesting that the Food and Drug Administration (FDA) determine whether Zometa (zoledronic acid for injection), equivalent to 4 milligrams (mg) base/vial lyophilized powder, has been withdrawn from sale for safety or effectiveness reasons.[1]

For the reasons described below, your petition is granted in part and denied in part.[2]

I. BACKGROUND

Zoledronic acid for injection is used for the treatment of hypercalcemia of malignancy. It also is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. In August 2001, FDA approved Novartis's new drug application (NDA) for Zometa (zoledronic acid for injection), equivalent to 4 mg base/vial, a lyophilized powder formulation (NDA 21-223) (powder formulation). In March 2003, FDA approved Novartis's supplement to the NDA for Zometa (zoledronic acid) injection, 4 mg base/5 milliliter (ml) concentrate solution formulation (NDA 21-223, Sup 004) (solution formulation). Novartis discontinued marketing the powder formulation in May 2003. Currently the powder formulation is listed in the "Discontinued Drug Products List" section of *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), 29th Ed., and the solution formulation is listed in the active "Prescription Drug Products List" section of the Orange Book.

[1] This citizen petition was originally assigned docket number 2007P-0341/CP1. The number was changed to FDA-2007-P-0250 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] You also submitted your request in the form of a *suitability petition* pursuant to 21 CFR 314.93. If, as you describe, the proposed generic product would be identical to the discontinued powder formulation without one of the changes described in § 314.93(b), the request is not appropriately submitted as a suitability petition. Therefore, your request to grant a suitability petition is denied.

FDA-2007-P-0250

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II. DISCUSSION

A. Discontinuation of Powder Formulation from Marketing

You request that FDA determine whether Zometa (zoledronic acid for injection), equivalent to 4 mg base/vial, a lyophilized powder formulation, approved in NDA 21–223 held by Novartis, was voluntarily withdrawn from sale for safety or efficacy reasons.

FDA has reviewed its records and determined that Zometa powder formulation was not withdrawn from sale for reasons of safety or effectiveness.[3] Thus, FDA will list Zometa (zoledronic acid for injection), equivalent to 4 mg base/vial, a lyophilized powder formulation, approved in NDA 21–223 held by Novartis in the "Discontinued Drug Product List" section of the Orange Book. This determination allows FDA to approve an abbreviated new drug application (ANDA) referencing Zometa powder formulation, as long as it meets the relevant legal and regulatory requirements for approval. See the enclosed copy of the *Federal Register* notice announcing the FDA determination. Therefore, this request is granted.

B. Safety of a Generic Referencing the Discontinued Formulation

You request that FDA make a determination that a proposed generic product referring to the originally approved powder formulation (now discontinued) would not render the product less safe or effective than the currently marketed innovator product (Petition at 1).

You describe the proposed generic product as identical to the discontinued Zometa powder formulation (Petition at 2-3). In one instance, you state that "[d]ue to unavailability of lyophilized form of RLD [reference listed drug] in the market, the liquid concentrate form has been considered as reference for the proposed labeling..." (Petition

[3] In 2003, FDA expressed concerns to Novartis about potential prescriber confusion were it to market both a powder and a solution formulation under the same trade name Zometa. FDA stated that if the parenthetical "(zoledronic acid for injection)" that accompanied the trade name were to be used for the powder formulation, the solution formulation somehow should be distinguished (e.g., "Zometa S (zoledronic acid injection)"). In part in response to these concerns, Novartis discontinued marketing the powder formulation in 2003. Upon further consideration, FDA believes that concurrent marketing of Zometa powder and solution formulations is not likely to pose a safety issue. Either form may be administered appropriately and safely, following proper instructions. The only difference is that the powder formulation requires two steps prior to administration, as opposed to the solution formulation which requires one final step. Both formulations are to be administered as an intravenous infusion over no less than 15 minutes with direct oversight by a healthcare professional. FDA has concluded that the difference between the powder and the solution is self-evident and that it is unlikely that the healthcare professional would confuse these two formulations. On numerous occasions, FDA has approved applications for both a powder and a solution formulation of the same drug product, contemporaneously marketed under the same name (see, e.g., Omnitrope (NDA 21-426 (solution and powder)), carboplatin (multiple ANDAs for solution (e.g., ANDA 77-247) and powder (e.g., ANDA 76-099)).

at 1); yet in another instance, you request FDA to make a determination that "the use of [the labeling from the powder formulation of Zometa] by the proposed generic product would not render the proposed generic product less safe or effective..." (Petition at 4).

If, as described in your petition, the proposed generic product is identical to the powder formulation, the discontinued powder formulation, and its labeling, would be the reference product. As stated above, we have concluded that the discontinued product was not withdrawn for reasons of safety or effectiveness. If a proposed generic product meets the relevant statutory and regulatory requirements for approval, we would expect the generic drug product to be as safe and effective as the discontinued Zometa powder formulation.

Because the proposed generic would reference the discontinued powder formulation, and not the currently marketed concentrate solution, it is unnecessary to assess comparative safety and effectiveness between the two formulations. Therefore, this aspect of your request is denied.

C. Therapeutic Equivalence Between a Generic Referencing the Discontinued Formulation and the Currently Marketed Formulation

You request that FDA determine that the proposed generic product "would be therapeutically equivalent to the currently marketed product" (Petition at 3).

We do not make therapeutic equivalence evaluations prior to approval. We note however that the Zometa powder formulation would be considered to be a different dosage form than the Zometa solution formulation because a dry powder to be reconstituted for injection is a different dosage form than an injectable solution. Two drug products are rated as therapeutic equivalents in the Orange Book only if, among other things, they are *pharmaceutical equivalents*, which is defined, in part, as being of the same dosage form (see page vi-vii of the preface of the Orange Book (29th Ed.)). A dry powder for injection would be considered a *pharmaceutical alternative* to an injectable solution, as described on page vii of the preface of the Orange Book (29th Ed.). (See also 21 CFR 320.1(c) and (d) for regulatory definitions of pharmaceutical equivalents and alternatives.)[4]

Therefore, your request to make a determination that the proposed generic is therapeutically equivalent to the currently marketed Zometa solution formulation is denied.

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[4] If an applicant sought to submit an ANDA for a zoledronic acid injection that is a solution formulation, referencing the powder formulation as the listed drug, the Agency would require an approved ANDA suitability petition for this change in dosage form under § 314.93 (see footnote 2). For example, a change in dosage form for carboplatin for injection (powder) to injection (solution) was approved in November 2001 (Legacy Docket No. 2001P-0036/CP1).

III. CONCLUSION

We have concluded that the discontinued Zometa powder formulation was not withdrawn for reasons of safety or effectiveness; therefore, FDA will accept ANDAs referencing this discontinued product. As a result, this aspect of your petition is granted.

For the above stated reasons, your requests for FDA to make a determination that the proposed generic would not be less safe and/or effective than, and would be therapeutically equivalent to, the currently marketed Zometa solution formulation are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Enclosure

address one or more of the following points: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the function of the agency, including whether the information will have practical utility; (2) Evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) Enhance the quality, utility, and clarity of the information to be collected; and (4) Minimize the burden of the collection of information on those who are to respond, including the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology.

FOR FURTHER INFORMATION CONTACT: To request more information on the proposed project or to obtain a copy of the data collection plans and instruments, contact: Joseph T. Hughes, Jr., Director, Worker Education and Training Branch, Division of Extramural Research and Training, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709 or call non-toll-free number (919) 541–0217 or E-mail your request, including your address to *wetp@niehs.nih.gov.*

Comments Due Date: Comments regarding this information collection are best assured of having their full effect if received within 60-days of the date of this publication.

Dated: April 2, 2009.

Marc S. Hollander,

NIEHS Associate Director for Management.

[FR Doc. E9–8472 Filed 4–13–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2007–P–0250] (formerly Docket No. 2007P–0341)

Determination That ZOMETA (Zoledronic Acid for Injection), Equivalent to 4 Milligrams Base Per Vial, Lyophilized Powder for Injection, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that ZOMETA (zoledronic acid for injection), equivalent to (EQ) 4 milligrams (mg) base/vial, lyophilized powder for injection, was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for zoledronic acid lyophilized powder for injection, 4-mg base/vial.

FOR FURTHER INFORMATION CONTACT: Nancy Boocker, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6244, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under 21 CFR 314.161(a)(1), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

ZOMETA (zoledronic acid for injection), EQ 4-mg base/vial, lyophilized powder for injection, is the subject of approved NDA 21–223 held by Novartis Pharmaceuticals Corp. (Novartis). Zoledronic acid, lyophilized powder for injection, EQ 4-mg base/vial, is indicated for treatment of hypercalcemia of malignancy. It also is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Novartis ceased manufacturing ZOMETA (zoledronic acid for injection), EQ 4 mg-base/vial, lyophilized powder for injection, in May 2003. On September 13, 2007, Kendle International, on behalf of Sun Pharmaceutical Industries Ltd., submitted a citizen petition (Docket No. 2007P–0341/CP1), under 21 CFR 10.30, requesting that the agency determine whether zoledronic acid lyophilized powder for injection, EQ 4-mg base/vial, was withdrawn from sale for reasons of safety or effectiveness.

The agency has determined that ZOMETA (zoledronic acid for injection), EQ 4-mg base/vial, lyophilized powder for injection, was not withdrawn from sale for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that zoledronic acid lyophilized powder for injection, 4-mg base/vial, was withdrawn from sale as a result of safety or effectiveness concerns. FDA's independent evaluation of relevant information has uncovered no information that would indicate this product was withdrawn for reasons of safety or effectiveness.

After considering the citizen petition and reviewing agency records, FDA determines that for the reasons outlined previously, ZOMETA (zoledronic acid for injection), EQ 4-mg base/vial, lyophilized powder for injection, was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list ZOMETA (zoledronic acid for injection), 4-mg base/vial, lyophilized powder for injection, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to ZOMETA (zoledronic acid for injection), EQ 4-mg base/vial, lyophilized powder for injection, may be approved by the agency as long as they meet all relevant legal and regulatory requirements for the approval of ANDAs. If FDA determines that the labeling of this drug product should be revised to meet current standards, the agency will advise ANDA applicants to submit such labeling.

Dated: March 7, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E9–8524 Filed 4–13–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of Federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Insect Salivary Proteins as Potent Adjuvants for Enhancing Immune Responses

Description of Technology: This invention relates to the discovery that specific sand fly salivary proteins have marked effects on the outcome of Leishmania infection. These proteins have the ability to stimulate strong Th1 and Th2 responses. The Th1 responses with one protein, PpSP15, result in immune protection while the Th2 responses to another protein, PpSP44, exacerbate infection. The protective protein enhanced a specific immune response to the infection, suggesting that it acts as an adjuvant to alter the environment and presentation of the parasite antigens.

These immunogenic salivary proteins, capable of driving Th1 or Th2 responses, can be used as adjuvants in vaccine development for a broad spectrum of diseases that require different immune responses. They may therefore be used to enhance immune responses to pathogens other than Leishmania parasites. They are also very potent in their effect, and small doses are sufficient to elicit a strong immune response. This potency can reduce the need to use chemical adjuvants, which often require large mounts of material and can have deleterious side effects.

Applications:

- Vaccine for Leishmania parasite and other pathogenic infections.
- Potent adjuvant for a broad spectrum of diseases.

Advantages: Efficient, potent, and less toxic than many chemical adjuvants.

Development Status: Early Stage.

Market:

- 88 countries with an estimated 2 million people affected each year.
- Estimated 350 million at risk worldwide.

Inventors: Jesus G. Valenzuela *et al.* (NIAID).

Publication: F Oliveira, PG Lawyer, S Kamhawi, JG Valenzuela. Immunity to distinct sand fly salivary proteins primes the anti-Leishmania immune response towards protection or exacerbation of disease. PLoS Negl Trop Dis. 2008 Apr 16;2(4):e226.

Patent Status: U.S. Provisional Application No. 61/089,884 filed 08 Aug 2008 (HHS Reference No. E–303–2008/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Jeffrey A. James PhD; 301–435–5474; jeffreyja@mail.nih.gov.

Collaborative Research Opportunity: The NIAID, Office of Technology Development is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the Insect Salivary Proteins as potent immune response adjuvants. Please contact Charles Rainwater at *crainwater@niaid.nih.gov* or 301/496–2644 for more information.

Anti-Cancer Oligodeoxynucleotides

Description of Technology: A majority of human cancers originate from epithelial tissue. A common cancer of epithelial cell origin is non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with more than seven hundred thousand (700,000) new cases diagnosed each year in the United States alone. BCC is rarely life-threatening because it is slow growing and is mostly localized. Unlike BCC, SCC metastasizes at a rate of two (2) to six (6) percent over several years after the initial diagnosis. A highly malignant form invades and destroys tissue, and then metastasizes, initially to a regional lymph node before more distant organs such as the lungs or brain are affected. SCC is commonly encountered in a number of epithelial tissues, including the oral cavity, esophagus, larynx, bronchi, intestines, colon, genital tract, and skin.

This application relates to suppressive CpG oligodeoxynucleotides (ODNs). This application claims suppressive ODN compositions and their use to prevent or delay the formation of a tumor, reducing the risk of developing a tumor, treating a tumor, preventing conversion of a benign to a malignant lesion, or preventing metastasis. Topical application of the ODNs of this invention in preclinical studies resulted in significantly fewer animals developing papillomas and fewer papillomas/animal. The invention also relates to use of suppressive ODNs to prevent/delay cancer when administered systemically as well as locally.

Application: Development of anti-cancer vaccines, therapeutics and diagnostics.

Development Status: ODNs have been synthesized and preclinical studies have been performed.

Inventors: Dennis M. Klinman and Hidekazu Ikeuchi (NCI)

Patent Status: U.S. Provisional Application No. 61/119,998 filed 04 Dec 2008 (HHS Reference No. E–296–2008/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The National Cancer Institute, Laboratory of Experimental Immunology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Neutralization of Hepatitis C Virus (HCV)

Description of Technology: Available for licensing and commercial development are compositions and methods for preventing and/or treating infection caused by hepatitis C virus (HCV). The invention is based on mapping studies conducted by the inventors of two epitopes within HCV E2: epitope I and epitope II. It has been discovered that epitope I is involved in virus neutralization but that epitope II mediates antibody interference,